

# Pyoderma gangrenosum – cutaneous and extracutaneous manifestations

## *Piodermia zgorzeliowa – skórne i pozaskórne manifestacje*

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### KEYWORDS:

- pyoderma gangrenosum
- extracutaneous manifestations
- cutaneous symptoms
- comorbidities

### ABSTRACT

Pyoderma gangrenosum (PG) is a rare, neutrophilic dermatosis with extracutaneous manifestations and associated systemic disorders, including inflammatory bowel diseases, arthritis and haematological malignancies. The pathogenesis of PG is still not fully understood. The cutaneous lesions are often polymorphic and include papules, nodules, sterile pustules with erythematous induration, which quickly evolve into necrotic painful ulcerations. PG can also affect lungs, spleen, liver, pancreas, kidneys, bones and eyes. The treatment of PG is long and challenging and involves the use of systemic corticosteroids, immunosuppressive drugs and biological therapies with concomitant pain management and wound care.

### SŁOWA KLUCZOWE:

- piodermia zgorzeliowa
- objawy skórne
- pozaskórne manifestacje
- choroby towarzyszące

### STRESZCZENIE

Piodermia zgorzeliowa jest rzadką dermatozą, charakteryzującą się naciekiem neutrofilów w skórze z wtórnym uszkodzeniem ścian naczyń. Dotychczas etiopatogeneza choroby nie została w pełni poznana, podkreśla się jednak rolę czynników immunologicznych. Zmiany skórne najczęściej lokalizują się na kończynach dolnych, początkowo pod postacią zapalnych guzków lub krost, szerzących się obwodowo z powstaniem owrzodzenia z martwiczym dnem. Oprócz objawów skórnych, obserwuje się także zajęcie innych narządów – płuc, śledziony, nerek, wątroby, trzustki, kości czy narządu wzroku. Szacuje się, że około 56,8% przypadków piodermii zgorzeliowej współwystępuje z innymi chorobami – w tym najczęściej nieswoistymi chorobami zapalnymi jelit, reumatoidalnym zapaleniem stawów oraz zaburzeniami hematologicznymi. W leczeniu piodermii zgorzeliowej stosuje się ogólne glikokortykosteroidy, klasyczne leki immunosupresyjne oraz leczenie biologiczne.

### Introduction

Pyoderma gangrenosum (PG) is a rare, ulcerative neutrophilic dermatosis with possible extracutaneous manifestations. Moreover, it is often associated with underlying systemic disorders, including inflammatory bowel diseases, arthritis, and hematological malignancies. PG was first described in 1930 by Brunsting, Goeckerman and O'Leary. They presented the theory, that PG had an infectious background with streptococcal or staphylococcal etiology. Over time the theory of bacterial origin was dismissed. Nevertheless, the name of the disease remained the same, as it was broadly accepted. Pyoderma gangrenosum can appear at any age with the peak of occurrence between 20 and 50 years. The incidence in infants and children's population is low and accounts for approximately 4% of all PG cases. Neither laboratory testing nor histopathological reports can confirm the diagnosis of pyoderma gangrenosum. Ruling out other

diseases with similar symptoms and clinicopathological correlation is necessary to verify the suspicion of PG (1-4).

### Pathogenesis

The pathogenesis of PG remains uncertain. Around 25-50% of cases of the disease are considered to be idiopathic. The concomitance of pyoderma gangrenosum with systemic diseases suggests immunologic and inflammatory pathologic response and genetic background. Massive infiltration of neutrophils, macrophages, and proliferation of clonal T-cells with secondary damage of the wall of the blood vessels have been found in the PG lesions. Activation of leukocytes, as well as growth factors, including granulocyte-macrophage colony-stimulating factor (GM-CSF) can stimulate the disease, which is connected with the dysfunction of neutrophils and uncontrolled infiltration leading to tissue destructions.

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Even trivial skin injuries, may lead to migration of leukocytes and activation of proteolytic enzymes and trigger symptoms of PG. Furthermore increased levels of cytokines have been detected by the immunohistochemistry methods in the skin lesions. Over-expression of TNF- $\alpha$ , IL-17, IL-1 $\beta$ , IL-8 and increased synthesis of matrix metalloproteinases (MMPs) have been found in PG, which play a significant role in the development of the inflammatory processes and cause damage to the tissue (2, 5-8).

### Clinical features

Since the histopathological findings and laboratory results of PG are nonspecific, the clinical examination plays the most important role in carrying out the diagnosis of pyoderma gangrenosum. Infiltration of neutrophils in PG leads to characteristic symptoms on the skin, and rarely in the other organs. The cutaneous lesions are polymorphic and in addition to the classic morphologic form of PG, several clinical subtypes of PG exist-vesiculobullous (atypical, bullous PG), pustular, superficial granulomatous pyoderma and pyostomatosis vegetativa, which differ according to symptoms, regions that are involved and comorbidities present. Although the skin lesions can occur in any location, including mucous membranes, in adults the most frequent site is lower extremities, whereas in children the head and anogenital region are more often involved. The primary skin manifestation of PG is usually tender, inflammatory papule, nodule or sterile pustule with erythematous induration, which could be misdiagnosed



Fig.1. Primary skin lesion in PG – reddish, inflammatory papule.



Fig.2. Ulceration with active border in patient with PG.

as furuncle or insect bite (Fig. 1). Subsequently, these lesions evolve quickly into painful necrotic ulcerations with erythematous-violaceous raised edge (Fig. 2, 3). The ulcers tend to expand towards the periphery and without treatment penetrate deeply exposing muscles, fascia, blood vessels, and nerves. The disease can have a fulminant course with general symptoms like fever, malaise or slow progression only with granulomatosis and effusion. Skin lesions resolve with cribriform scarring. The characteristic symptom, which occurs in 20-30% of patients with PG is pathergy – small injuries can trigger and exacerbate the skin lesions (1, 2, 9-11).

### Extracutaneous manifestations and underlying systemic diseases of PG

Even though the most common site of pyoderma gangrenosum is in the skin, mucosal and extracutaneous manifestations have also been observed. PG can affect the lungs, spleen, liver, pancreas, kidneys, and bones. Moreover, involvement of the eye and periorbital area has been reported, leading to ulceration, peripheral ulcerative keratitis, retinal vasculitis and decreased visual acuity. Pulmonary manifestations are rare, manifesting as nodules with or without cavitation, interstitial lung disease, pleural effusions and could be potentially associated with a severe course of the disease. Chronic, multifocal osteomyelitis has been observed in some cases of pyoderma gangrenosum, which is often related to inflammatory bowel disease (1, 2, 4, 12-17).

It has been estimated, that approximately 56,8% of cases with PG are associated with other systemic diseases. Amongst systematic reviews, most common comorbidities include inflammatory bowel diseases (17,6%), polyarthritis (12,8%), hematological disorders (8,9%) and solid malignancies (7,4%). PG is the second most frequent cutaneous manifestation of inflammatory bowel diseases, occurring more often in ulcerative colitis than in Crohn's disease. In addition to the above, psoriasis, acne and hidradenitis suppurativa could be associated with PG, presenting with rare syndromes – PAPA (pyogenic arthritis, PG, acne), PAPAASH (pyogenic arthritis, PG, acne, suppurativa hidradenitis) or PsAPASH (psoriatic arthritis, pyoderma gangrenosum, acne, suppurativa hidradenitis). The underlying systemic diseases have a significant impact on the course of the illness and should be taken into account during the choice of treatment (1, 2, 4, 18) .



Fig. 3. Superficial ulceration and active primary skin lesion in PG.

## Treatment

The management of pyoderma gangrenosum is challenging and often requires also treatment of the associated diseases, although the direct correlation between the severity of comorbidity and PG has not been proven. The choice of treatment should take into consideration many aspects including number, intensity, and location of lesions, extracutaneous manifestations, associated diseases and adverse effects of the therapy. The treatment is mainly based on immunosuppression. The systemic corticosteroids – usually oral prednisone (0.5-1 mg/kg/day) are the first-line therapy for pyoderma gangrenosum. Cyclosporine and TNF- $\alpha$  inhibitors are considered as second – and third-line therapies in severe cases of PG or with ineffective primary treatment with corticosteroids. The other immunosuppressive agents including cyclophosphamide, methotrexate, mycophenolate mofetil, sulfasalazine, and azathioprine have also been effective in some cases of PG. Recently, the studies have suggested the role of biologic therapy, particularly TNF- $\alpha$  (infliximab, adalimumab) and IL-1b inhibitors (canakinumab) in the treatment of PG. Systemic therapy should be complemented by proper pain management and wound care (2, 19-22).

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